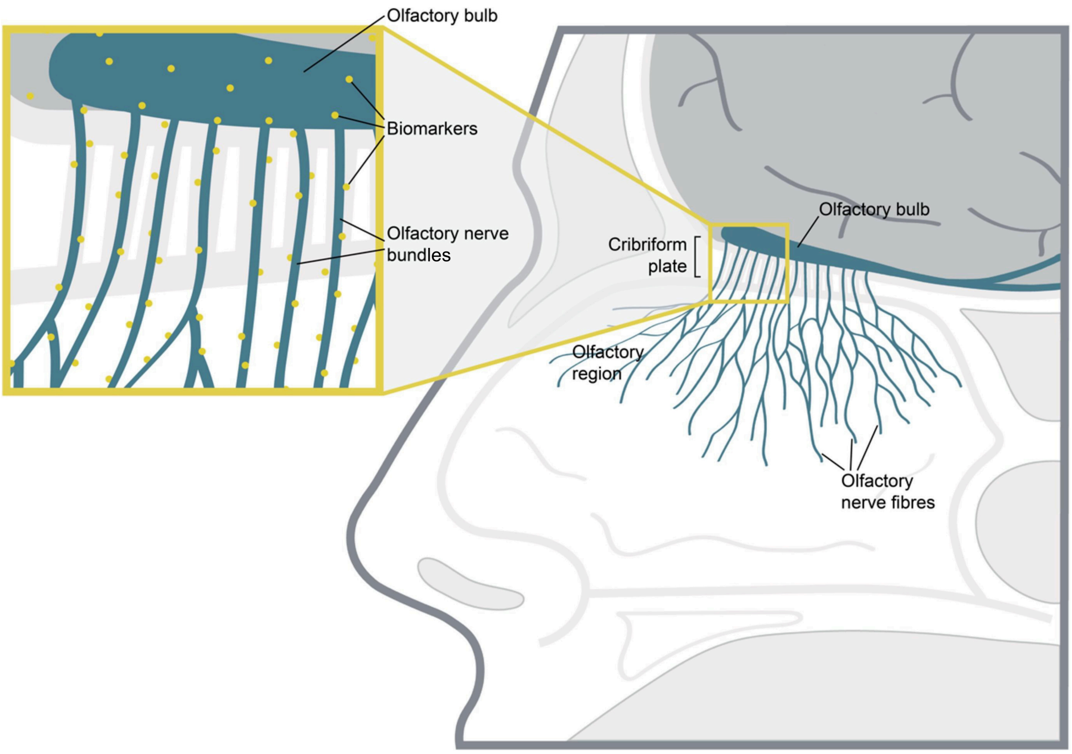
White Paper

The Brain-Nose Interface: A New Path to Assess Brain Health

The human brain remains one of the most difficult organs to study. Direct access to the brain is limited because it is protected within the skull. Brain imaging, analysis of cerebrospinal fluid (CSF) collected through lumbar puncture, and tissue biopsies provide valuable information about brain health. At the same time, these methods are costly or invasive, and not practical to repeat frequently. Blood tests for brain disorders are improving rapidly, but they still face basic biological limitations as the blood-brain barrier restricts most brain-derived molecules from readily entering the bloodstream, and the blood carries signals not just from the brain but also from the entire body.

There is an alternate route around this barrier called the brain-nose interface (BNI). The BNI is a direct connection between the brain and the upper nasal cavity created by the unique anatomy at this region. The part of the skull at the BNI that separates the brain from the nose (known as the cribriform plate), contains tiny sieve-like openings. Through these openings, millions of olfactory nerve fibers pass from the upper nasal cavity to the brain, establishing a direct connection. Although this anatomy was historically viewed as important mainly for faster smell processing, it is now recognized to play an important role in the movement of fluid and molecules from the brain to the nose. A key fluid exchange process across the BNI is the



The brain-nose interface (BNI). The BNI is the anatomical junction where the brain connects directly with the nose, separated only by the perforated cribriform plate. Olfactory nerve fibers pass through the small openings in the cribriform plate, connecting the olfactory region in the nasal cavity to the olfactory bulb in the brain. Brain-derived molecules (yellow dots) move along the olfactory nerve fibers into the upper nasal cavity, where they can be collected through minimally invasive sampling. (Reproduced from San Nicoló et al., Methods 234 (2025): 233-241) drainage of CSF from the brain, which creates a route for brain-derived molecules to reach the nose. CSF is involved in the uptake and removal of metabolic byproducts, cellular debris, and disease-associated proteins from the brain, and recent studies have shown that their removal occurs through the drainage of CSF along the olfactory nerve fibers to the upper nasal cavity. Through this drainage pathway, disease biomarkers, including amyloid-beta and tau in Alzheimer's disease or alpha-synuclein in Parkinson's disease, can reach the nose. Thus, the BNI allows for minimally invasive access to brain-related molecules by sampling through the nose.

The BNI has long attracted attention in neurodegenerative diseases as the olfactory system is often affected early in the disease process. In diseases such as Alzheimer's and Parkinson's, changes in smell perception can appear years, and sometimes even decades, before clinical symptoms. Along with these early sensory changes, disease-related protein pathology has also been found in both olfactory-related brain regions and nasal tissues. The combination of pathology at the BNI and the direct fluid drainage carrying brain-derived material creates a unique opportunity to access brain health through minimally invasive sampling of upper nose. Early studies support this concept, showing that disease-related proteins in nasal samples can distinguish patients with Alzheimer's disease, Creutzfeldt-Jakob disease, and synucleopathies from controls. This nasal sampling approach overcomes limitations of CSF sampling, which is invasive and not easily repeatable, as well as blood testing, which is constrained by the blood-brain barrier and signal interference originating outside the brain.

The use of the BNI for brain biomarker collection is further supported by its well-known role in direct drug delivery from the nose to the brain. Direct intranasal drug delivery to the brain has moved from a preclinical concept to early clinical use in patients. The nasal pathway improves drug transport to the brain by reducing their systemic exposure when compared to oral or intravenous intake. Together, the BNI's role in CSF drainage from brain to nose and in drug transport from nose to brain highlights its bidirectional transport properties, underscoring its potential for both diagnosis and therapy.

In summary, the BNI opens a direct, minimally invasive window to the brain through the nose. Nasal sampling could therefore enable repeated diagnostic testing, allowing early screening and intervention, as well as longitudinal monitoring of disease progression and treatment response. Important questions regarding the BNI still remain, such as the complexity of the nasal environment, the exact mechanism by which molecules move across the BNI, and its clinical usefulness. Nevertheless, the overall outlook for the BNI in brain diagnostics is promising. As the field advances, this route could become a practical tool for understanding, monitoring, and improving brain health.

References

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